REMARKS

Claim 1 has been amended to recite "[a] fermentation method of astaxanthin using Phaffia rhodozyma comprising the steps of: (a) in the growing phase, feeding of a nutrient medium containing glucose or sucrose based on the specific growth rate (μ) of *Phaffia rhodozyma* cells, and (b) in the astaxanthin production phase, feeding of the nutrient medium based on the astaxanthin production rate, while keeping the glucose concentration in the fermentation broth at ~~almost~~ 0 g/L during the whole fermentation period." Support for this amendment is found throughout the specification at, for example, page 7, line 32 to page 8, line 3; page 16, lines 9-24; and in original claim 1. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01(o) and (l) (8th ed. Rev. 6, Sept. 2007, pp. 600-92 and 600-84).

Claim 7 has been amended to place the claim in a more appropriate format. The amended claim recites "[t]he fermentation method according to claim 1, wherein the nutrient medium ~~contains as~~ has at least one carbon energy ~~sources~~ source selected from the group consisting of polymerized forms of glucose, sucrose and other polysaccharides, molasses and corn syrup, glycerol and other polyols, and carboxylic acids, and, ~~as~~ at least one nitrogen ~~sources,~~ source selected from the group consisting of yeast extract, meat-extract, peptone, casein, corn steep liquor, urea, amino acid, nitrates, and ammonium salts ~~and the like~~. Support for this amendment is found in the specification at, *e.g.*, page 3, lines 8-22. For example, the specification discloses with regard to the possible components of the nutrient medium that "[t]he combinations and concentrations of these materials ... can vary to convenience." Page 3, lines 12-14. Furthermore, the specification discloses that "[t]he nutrient

medium ***can*** contain polymerized forms of glucose, sucrose and other polysaccharides, molasses and corn syrup, glycerol and other polyols, carboxylic acids..." and it "***can*** contain yeast extract, meat-extract, peptone, casein, corn steep liquor, urea, amino [acids nitrates], ammonium salts...". Page 3, lines 19-21. Accordingly, it is submitted that the Markush language of the amended claim is proper. It is also noted that we have deleted the phrase "and the like" at the end of claim 7. Furthermore, the specification discloses that the nutrient medium may include ingredients other than the carbon source and nitrogen source, for example, "various vitamins and minerals" and "an antifoam agent and/or other additives". Page 3, lines 8-12 and lines 14-15. As such, deleting the closed-ended claim transitional phrase, "contains", which makes reference to the "nutrient medium", and replacing it with the open-ended transitional phrase "has" is appropriate and well-supported by the specification.

It is submitted that no new matter has been introduced by the foregoing amendments. Approval and entry of the amendments is respectfully solicited.

INTERVIEW SUMMARY

The Examiner is thanked for the courtesies extended during a telephonic Interview conducted on March 4, 2008 with the undersigned who is acting in representative capacity under 37 CFR § 1.34, and Charles M. Avigliano, Reg. No. 52,578, an attorney of record ("Examiner's Interview"). During the Examiner's Interview, the amendment to claim 1 and the pending §103 rejection were discussed. The Examiner agreed that the amendment presented to claim 1 would likely place the application in condition for allowance. The Examiner's Interview Summary, Paper No.

20080304, indicates that "[u]pon receipt of the amendment to the claims, this limitation will be considered favorably for allowability ..." (Page 2.) We note that the amendment discussed and presented here to claim 1 recites "keeping the glucose concentration in the fermentation broth at ~~almost~~ 0 g/L during the whole fermentation period." Stated otherwise, the word "almost" is replaced with "at". The Examiner stated in the Interview Summary that the proposed amendment is to replace the term "almost" with ---is--- "0 g/L". (Id.) The actual proposal to use the word "at" rather than ---is--- imparts the same meaning but is grammatically correct in usage in the claim. Accordingly, it is believed that the Examiner has agreed to the same substantive claim amendment as proposed.

During the Interview, steps (a) and (b) of claim 1 were discussed, each of which encompass a different phase of the cells, namely "the growing phase" and "the astaxanthin production phase", respectively. We wish to direct the Examiner's attention to the fact that claim 1 recites "***[a] fermentation method*** of astaxanthin using Phaffia rhodozma..." The amended portion at the end of claim 1 which recites, "keeping the glucose concentration in the fermentation broth at ~~almost~~ 0 g/L ***during the whole fermentation period***" refers to the glucose concentration during the whole fermentation period which encompasses both recited phases, i.e., "the growing phase" and "the astaxanthin production phase".

In view of the amendments above and the remarks below, withdrawal of the rejection and allowance of the claims are respectfully requested.

Obviousness Rejections:

Claims 1-10 have been rejected solely under 35 USC § 103 as being unpatentable over Jacobson *et al.*, U.S. Patent No. 6,015,684 ("Jacobson"), or further in view of Derwent Abstract, Choi *et al.*, KR Patent Publication 2001044210 ("Choi"). (Paper No. 20071017 at 2).

Jacobson discloses "*Phaffia rhodozyma* strains ... which produce greater than 3,000 ppm astaxanthin based on dry yeast solids when cultivated in a volume of nutrient medium of at least about 1,500 liters and containing in excess of 4 percent, preferably in excess of 6 percent, dry yeast solids." (Abstract). Jacobson further discloses that "[t]hese and other strains are cultivated by an improved fermentation method comprising extending the maturation phase of the fermentation by one or more various techniques including exposing the yeast cells to a low-intensity light, slow feeding the cells with a rapidly metabolized energy source, e.g. glucose, and replacing the rapidly metabolized energy source with a slowly metabolized energy source, e.g. gylcerol." (*Id.*)

In making the rejection, the Examiner asserted that Jacobson "teaches" the following:

> Start-up conditions are 8 standard liters per minute (SLPM) aeration and 500 rpm agitation. The pH is controlled at 5.5 with 750 ml 1:3 dilution of reagent grade ammonium hydroxide, NH_4OH. Food grade antifoam is added as required. The culture is fed 1750 g glucose (Cerelose™, CPC International, Summit-Argo, Ill.) as a 50% by weight solution at a rate such that the glucose concentration is less than 5 grams per liter (g/l), preferably between 0.1 and 2.5 g/l throughout the fermentation. Dissolved oxygen is controlled by agitation and airflow to between 20% and 90% saturation. Results of such fermentations with UBV-AX3 and

> 4 are presented in Table 1. (Paper No. 20071017 at 2-3) (emphasis original).

The Examiner further asserted that the above disclosure "renders the claimed language prima facie obvious for claim 1 ... since it is considered that 0.1 g/L is almost 0 g/L." (*Id.* at 3).

The Examiner then asserted that "[i]f there are any other differences with respect to the μ range, pH, temperature, concentration, nutrients, reagents employed for controlling the pH or gassing rates, these conditions based on the disclosure of Jacobson et al would have been prima facie obvious for one skilled in the art absent unexpected results or process steps." (*Id.*).

With regard to claim 10, the Examiner asserted that "the microorganism employed in the production of astaxanthin would have been prima facie obvious to substitute for the microorganism of Jacobson et al in view of the advantages taught by Choi whereby the microorganism strain generates astaxanthin in a high yield in a short period of time which would be prima facie obvious for one of ordinary skilled in the art to reasonably expect to obtain higher yields in a shorter time using the strain of Choi in the process of Jacobson et al absent unexpected results." (*Id.*).

It is well settled that the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to modify the document(s) relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to modify a reference must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion to modify the reference(s) should "***be based on objective evidence of record***." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added); *see also In re Kotzab*, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000).

Here, the rejection is devoid of *any* evidence - or even argument - in support of the proposed modification. All that is there is a conclusory remark that "the claimed language [is] prima facie obvious for claim 1 ... since it is considered that 0.1 g/L is almost 0 g/L." (Paper No. 20071017 at 3). What the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify the disclosure of Jacobson either alone or in view of Choi to arrive at the claimed invention. As is well settled, an Examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, *12 (Fed. Cir. June 28, 2007) (indicating that "it remains

necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Moreover, the Examiner's assertion that "[i]f there are any other differences with respect to the μ range, pH, temperature, concentration, nutrients, reagents employed for controlling the pH or gassing rates, these conditions based on the disclosure of Jacobson et al would have been prima facie obvious for one skilled in the art absent unexpected results or process steps" is against the Board's own precedent. (Paper No. 20071017 at 3). The Board has already addressed and settled this issue by reversing a rejection based on the same premise. *See, e.g., Ex parte Daddario*, 2002 WL 33944182, *5 (BPAI 2002) (unpublished) (reversing an examiner's §103 rejection and stating that "the examiner has relied on the theory that the ***selection of temperatures and pressures*** would have been matters of choice that would have 'obviously been determined ... through routine optimization.'" "However, ***the examiner has not directed our attention to any factual basis in the prior art of record supporting these determinations***. As our reviewing court has repeatedly emphasized, '[t]he Board's findings must extend to all material facts and must be documented on the record, lest the 'haze of so-called expertise' acquire insulation from accountability. 'Common knowledge and common sense,' even if assumed to derive from the agency's expertise, do not substitute for authority when the law requires authority. *In re Lee*, 277 F.3d 1338, 1344-45, 61 USPQ2d 1430, 1435 (Fed. Cir.

2002)." "For this reason, we are constrained to reverse the rejection of claims 17-19.") (emphasis added). For this additional reason, the rejection should be withdrawn.

Notwithstanding the legally insufficient nature of the rejection, we note that the rejection is also factually insufficient to support a rejection under § 103(a). In doing so we observe that obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, ***all claim limitations must be taught or suggested by the prior art***." MPEP § 2143.03 (citing *In re Royka*, 180 USPQ 580 (CCPA 1974)) (emphasis added).

As noted above, claim 1 has been amended to recite "[a] fermentation method of astaxanthin using Phaffia rhodozyma comprising the steps of: (a) in the growing phase, feeding of a nutrient medium containing glucose or sucrose based on the specific growth rate (μ) of *Phaffia rhodozyma* cells, and (b) in the astaxanthin production phase, feeding of the nutrient medium based on the astaxanthin production rate, ***while keeping the glucose concentration in the fermentation broth at ~~almost~~ 0 g/L during the whole fermentation period***."

As noted above, Jacobsen characterize their disclosure as providing "an improved fermentation method comprising ***extending the maturation phase*** of the fermentation by one or more various techniques..." Abstract. (emphasis added). Jacobsen characterizes their technique involving glucose feeding as "slow feeding the

cells with a rapidly metabolized energy source, e.g., glucose..." (Abstract). As noted by the Examiner, Jacobsen disclose that the medium "preferably" has an energy source present "between 0.1 and 2.5 g/l throughout the fermentation." Column 11, lines 32-34.

Jacobsen disclose that during the growth phase, "the yeast cells are provided with a controlled amount of a rapidly, relative to a polysaccharide, metabolized energy source, e.g., glucose or sucrose. " Column 7, lines 30- 36. Jacobsen disclose that while "the yeast cells are fed this energy source", it should "not accumulate in the nutrient medium to any substantial extent." Column 7, lines 32-36. Jacobsen further disclose that "[t]he accumulation of the energy source in the medium is generally a signal that the growth phase is ending and the maturation phase is beginning." Column 7, lines 38-41. Jacobsen disclose reducing the feed rate of the energy source by "at least about 50%...of the maximum feed rate during the growth phase" from "[a]fter the desired yeast solids is achieved and prior to the accumulation of the energy source..." Column 7, lines 42-46. Furthermore, Jacobsen disclose that "[t]o maximize the accumulation of astaxanthin during the maturation phase, the energy source feed rate can be reduced in a step-wise or continuous manner. For example, with the onset of the maturation phase, the energy source feed rate can be reduced by 50% and after a certain period of time, typically 12 to 24 hours, it can be reduced another 50%." Column 7, lines 52-57.

In view of the disclosures of Jacobsen, one skilled in the art would not consider Jacobsen as teaching or suggesting to keep the "glucose concentration in the fermentation broth at 0 g/L ***during the whole fermentation period***" as recited in amended claim 1. There is no disclosure that would indicate to one skilled in the art

maintaining a glucose concentration of 0 g/L throughout the fermentation period. Nor does Jacobsen provide enabling disclosure to achieve this.

Here, Jacobson, either alone or in view of Choi, does not disclose or suggest the fermentation method currently claimed. First, the Examiner does not mention or discuss, much less point to any disclosure in Jacobson or Choi regarding step (a) of claim 1, which recites "in the growing phase, feeding of a nutrient medium containing glucose or sucrose based on the specific growth rate (μ) of *Phaffia rhodozyma* cells ...." Feeding the energy source "as rapidly as possible with the proviso that it does not accumulate in the nutrient medium to any substantial extent", as disclosed by Jacobsen, Column 7, lines 32-33, fails to teach or suggest use of a specific growth rate (μ) of the cells, as claimed.

Furthermore, the Examiner does not mention or discuss, much less point to any disclosure in Jacobson or Choi regarding step (b) of claim 1, which recites "in the astaxanthin production phase, feeding of the nutrient medium based on the astaxanthin production rate...". Jacobsen discloses that "with the onset of the maturation phase, the energy source feed rate can be reduced by 50%..." Column 7, lines 54-56 and 42-51. This reduction is based upon the previous feed rate, i.e., it is **"reduced to at least about *50%, preferably at least about 40%, more preferably at least about 30%, of the maximum feed rate during the growth phase.*"** Column 7, lines 44-46 (emphasis added). Merely setting the reduction to a certain percentage reduction based on maximum feed rate does not suggest feeding the nutrient medium based on the astaxanthin production rate.

Furthermore, Jacobsen does not suggest keeping the glucose concentration at 0 g/L during the astaxanthin production phase nor, tellingly, during the whole fermentation period. In fact, where Jacobsen makes reference to both "the reduced energy source technique", *e.g.*, slow feeding of glucose, and feeding more slowly metabolized extenders during the maturation phase, e.g., polymerized forms of glucose, sucrose, etc., Jacobsen disclose that "**these extenders are fed to the yeast cells at the time energy source (*e.g.* glucose) accumulation is detected**...". Column 8, lines 1-4 (emphasis added). One skilled in the art would understand that Jacobsen uses the accumulation of glucose in the cell media as a signal that the growth phase has ended. This certainly does not suggest keeping the glucose concentration at 0 g/L during the whole fermentation period. In fact, it leads one skilled in the art away from the presently claimed fermentation parameters. As is well settled, to do what the prior art teaches against is the very antithesis of obviousness. See, *e.g.*, *In re Rosenberger*, 156 USPQ 24, 26, (CCPA 1968) and *In re Buehler*, 185 USPQ 781, 787 (CCPA 1975).

Jacobsen provides no suggestion or motivation to achieve the claimed fermentation method. The Examiner provides no reason why one skilled in the art would modify the disclosed parameters of Jacobsen to achieve glucose at 0 g/L in the medium throughout the fermentation period. Furthermore, Jacobsen provides no such reason. And, as set forth in more detail below, the rejection is silent as to what, if anything Choi adds to this gap in Jacobsen.

In addition, the claimed method achieves improvements and advantages that are not even hinted at by Jacobson. The present application discloses that when

no glucose is accumulated in the culture broth, "total astaxanthin production by this method can be enhanced more than 12% higher than that by the control method." Paragraph 31, lines 2-9. Furthermore, this method "can shorten the fermentation period (at least 11% of the fermentation period can be cut down in the comparison with the control method) and enhance the astaxanthin productivity." Paragraph 32, lines 6-10.

As noted, however, the teachings of Jacobsen involve ***extending the maturation phase***. Jacobsen acknowledges that the techniques disclosed "will extend this [maturation] period." Column 8, lines 25-26. Jacobsen provide no suggestion or motivation to attempt a fermentation method that can achieve an overall shorter fermentation period, as in the claimed invention. In fact, Jacobsen's disclosure leads one skilled in the art away from attempting a method to achieve a shorter fermentation period. As is well settled, to do what the prior art teaches against is the very antithesis of obviousness. See, *e.g.*, *In re Rosenberger*, 156 USPQ 24, 26, (CCPA 1968) and *In re Buehler*, 185 USPQ 781, 787 (CCPA 1975).

For each of the foregoing reasons, it is submitted that the rejection based upon Jacobsen is deficient and should be withdrawn. Reconsideration and withdrawal of the rejection are requested.

The rejection over Jacobsen alone is also devoid of any discussion of the dependent claims, other than claim 10 and that relates only to the combination of Jacobsen with Choi. Accordingly, the record is devoid of any evidence that the Examiner individually considered any of the dependent claims in connection with the rejection over Jacobsen alone. It is axiomatic, however, that a dependent claim is not

per se unpatentable by a document that allegedly makes unpatentable the base claim. Accordingly, "[e]xaminers are reminded that a dependent claim is directed to a combination including everything recited in the base claim and what is recited in the dependent claim. ***It is this combination that must be compared with the prior art, exactly as if it were presented as one independent claim.***" MPEP § 608.01(n) (8th ed., Rev. 5, Aug. 2006, pp. 600-91). This the Examiner has not done. Accordingly, the rejection is both factually and legally deficient as to the other dependent claims. For this additional reason, the rejection should be withdrawn as to all of the dependent claims.

Also, it is submitted that Jacobsen in combination with Choi is an improper rejection. And, if the rejection based on the combination of Jacobsen and Choi were proper, it is submitted that it fails to render the claims obvious.

Remarks and arguments concerning Jacobsen made above are incorporated here in their entirety.

Choi discloses "a method for separating mutant strain, Phaffia rhodozyma (KCTC-0920B) which generates astaxanthin in a high yield in a short period of time without being degenerated into a wild type during continuous cultivations." (Derwent Abstract). Choi further discloses that "[t]he method for separating mutant strain, Phaffia rhodozyma (KCTC-0920B) comprises the steps of: i) cultivating Phaffia rhodozyma (ATCC-96594) in YM broth and treating the strain with 1-methyl-3-nitro-1-nitrosoguanidine (NTG) to kill 98% of yeast; ii) spreading the remaining yeast on YM medium for cultivation and selecting colonies which are growing faster with red color *than the original strain*; iii) repeating these processes several times and then, cultivating

selected bacteria in YM broth for 4-6 days; and iv) measuring the amount of mycobiont and carotenoid and selecting the strain which produces carotenoid in a high yield." (*Id.*) (emphasis added).

The Examiner relied on Choi as disclosing a "microorganism strain [that] generates astaxanthin in a high yield in a short period of time which would be prima facie obvious for one of ordinary skilled [sic] in the art to reasonably expect to obtain higher yields in a shorter time using the strain of Choi in the process of Jacobson et al absent unexpected results." (Paper No. 20071017 at 3.) The Examiners' statements concerning Choi are made only with reference to claim 10. (Id.)

It is submitted that the rejection over Jacobsen in view of Choi is not applicable to claims 1-9, as the Examiner has made no comments concerning Choi pertaining to any of these claims. To forward prosecution in this matter, however, the following comments pertain to claims 1-10.

The Examiner's reliance on Choi is misplaced, whether with regard to claim 10 alone or to all pending claims.

Choi makes no mention of cell feeding methods and fails to provide any suggestion or motivation to attempt a fermentation method in accordance with the claimed method. With no relevance to cell feeding techniques, it is submitted that Choi is not a proper document to cite as a basis for rejection.

Furthermore, if Jacobsen and Choi are combined as proposed by the Examiner, which Applicants maintain is improper, then all that may result is the feeding method of Jacobsen which may use the P. rhodozyma ATCC96594 strain or another P. rhodozyma strain, further involving continuous cultivations of the cells to separate

mutant strains. One skilled in the art, viewing the combined documents, would still not be led to the claimed fermentation method in which the glucose concentration in the fermentation broth is kept at 0 g/L during the whole fermentation period. Hence, the proposed combination of Jacobson alone or in view of Choi falls short of disclosing or suggesting the currently claimed invention.

In view of the foregoing, the rejection over Jacobsen in view of Choi as to claim 10 (and as to claims 1-9, if such rejection was properly applied to these claims), is rendered moot. Withdrawal of the rejection is requested.

Accordingly, for the reasons set forth above, entry of the amendments, withdrawal of the rejection, and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on March 24, 2008.

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